Original Article

An Aggressive Strategy for Maintenance of Sinus Rhythm Including a Combination of Catheter Ablation and Antiarrhythmic Drug Therapy Benefits Patients with Chronic Atrial Fibrillation

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The effects of restoration and maintenance of sinus rhythm by a combination of catheter ablation and antiarrhythmic drugs (AADs) on atrial function in patients with chronic atrial fibrillation (AF) remain unknown. In 15 patients with chronic AF (>1 year), we attempted to restore and maintain sinus rhythm by ablation targeting complex fractionated atrial electrocardiograms (CFAEs) combined with pulmonary vein isolation with or without AADs. Sinus rhythm was restored in all patients. At 17.7 ± 7.2 months after AF ablation, maintenance of sinus rhythm was achieved in 20% of patients without AADs and in 73.3% of patients with AADs. The left atrial diameter decreased significantly by $9.5 \pm 8.1\%$ ($P < 0.05$) during the 12-month followup. AADs did not have any adverse effects. The aggressive strategy for maintenance of sinus rhythm involving AF ablation and AADs potentially led to recovery of structural changes in the LA in patients with chronic AF.
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Key words: Chronic atrial fibrillation, Ablation, Atrial function

Introduction

Atrial fibrillation (AF) tends to be a chronic condition, and thereby potentially leads to functional and structural changes in both atria.[1–7] Recent studies have reported that various techniques, including extensive circumferential pulmonary vein isolation, AF ablation targeting complex fractionated atrial electrograms (CFAEs), and stepwise ablation, enable the restoration and maintenance of sinus rhythm in patients with chronic AF.[8–11] Regardless of pharmacological or non-pharmacological therapy, maintenance of sinus rhythm during long-term follow-up has been shown to be associated with a reduction in the left atrial (LA) diameter.[11–14]

In contrast, the RACE trials revealed that antiarrhythmic drug (AAD) therapy alone is incapable of fully maintaining sinus rhythm in patients with persistent AF, and furthermore, can potentially lead to adverse effects.[15] We attempted to restore and maintain sinus rhythm in patients with chronic AF (>1 year) by performing CFAE ablation combined with pulmonary vein (PV) isolation with or without AAD therapy. The aim of the present study was to

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assess whether our aggressive strategy benefits patients with chronic AF.

Methods

Study Population

Fifteen consecutive patients with chronic AF referred for AF ablation were studied. In the present study, chronic AF was defined as AF lasting >1 year (range, 1.5–13 years) and resistant to AAD and/or DC cardioversion.

Preablation procedure

All patients were administered international normalization ratio-based (2.5 > INR > 1.5) oral anticoagulant therapy for 2 months. The oral anticoagulant therapy was substituted with heparin infusion for 2 days before AF ablation. AAD and/or β blocker therapy was discontinued at least 5 half-lives before the procedure.

All patients were subjected to transesophageal echocardiography to exclude the presence of a thrombus in the LA, to measure the peak flow velocity at the ostium of the left atrial appendage, and to observe the anatomy of the atrial septum. Written informed consent was obtained from all patients.

Swan-Ganz catheterization was performed before and immediately after AF ablation in 10/15 patients in order to assess the changes in the hemodynamic parameters.

Ablation procedure

For recording and pacing, a decapolar catheter (Inquiry Luma; Irvine Biomedical, USA) was placed in the coronary sinus, and quadripolar catheters (M-sweep; Daig, USA) were placed high in the right atrium (RA) and the apex of the right ventricle.

An intracardiac phased-array ultrasound catheter (Ultra ICE, Boston, USA) was placed in the RA to guide trans-septal puncture. After trans-septal puncture, heparin was infused intravenously as a bolus of 5000 U and was continuously administered to achieve an activated clotting time (ACT) of 300 to 350 seconds during AF ablation. A 4-mm-tip deflectable catheter (NaviStar, Biosense Webster, USA) and 2 decapolar circular catheters (Lasso; Biosense Webster, USA, and Optima; Irvine Biomedical, USA) were advanced to the LA and placed in the ostium of each pulmonary vein for mapping and ablation.

A 3D electroanatomical map of the LA, including the PV ostia, the ostium of the LA appendage, and the mitral annulus, was constructed using the NaviStar catheter and a nonfluoroscopic navigation system (CARTO; Biosense-Webster, USA). All sites where CFAEs were identified during LA mapping were tagged on the 3D CARTO map.

Based on the description of Nademanee et al.,[10] CFAEs were defined as (1) atrial electrograms with 2 or more deflections and/or fluctuation from the baseline and/or continuous electrical activity over a 5-second period, or (2) atrial electrograms with very short cycle length activity (<120 msec) over a 5-second period. Bipolar electrograms were recorded using the NaviStar catheter and filtered at a bandpass of 30 to 500 Hz.

Prior to application of radiofrequency (RF) energy, the borders of the esophageal lumen were visualized by fluoroscopy after the patient had swallowed 10 ml of a contrast medium (Gastrografin; Bayer Schering Pharma, Germany).

Ablation was performed using the Navistar catheter and/or an 8-mm tip ablation catheter (Fantasista; Japan Lifeline, Japan) in the temperature-control mode with guidance from the CARTO system, PV angiograms, and the 3D-computed tomogram. For PV isolation, RF was delivered to the LA-PV junctions approximately 0.5 to 1 cm outside of the PV ostium as defined on angiography. For RF delivery, we set a maximum temperature of 55 °C (50 °C at the sites close to the esophagus) and a maximum power of 25 W (for the posterior aspect of the left PV ostium close to the esophagus) to 35 W for up to 60 seconds. In sites where the RF output did not rise up to 10 W, the 8-mm tip ablation catheter was used. The end point of PV isolation was abolition or dissociation of electrical activity in all the PVs.

The endpoint for CFAE ablation was conversion of the CFAEs to discrete electrograms or approximately >25% prolongation in the local cycle length at each site. RF was delivered for 30 s at a maximum temperature of 50 °C and the maximum power output of 30 W to each site where CFAEs were identified in the LA. Unless AF was terminated through CFAE ablation in the LA, CFAE ablation was additionally performed in the RA by the same technique and up to the same endpoint as that for the LA. If AF persisted even after CFAE ablation in both atria, DC cardioversion was used to restore sinus rhythm.

After restoration of sinus rhythm, the bidirectional conduction block between the PV and LA was confirmed by circumferential pacing at the ostium of each PV. If any residual PV-LA conduction was found, RF was delivered to the conduction gap under the guidance of circular catheters placed in the

Table Baseline Characterisitics of Patients

Age (years)	58.2 ± 7.2
Gender (male/female)	14/1
AF duration (year)	range 1–13
Failure in electrical cardioversion (%)	40.0, 6/15
NYHA classification	1.3 ± 0.6
Structural heart disease (%)	
Hypertensive cardiomyopathy	20, 3/15
Dilated cardiomyopathy	13, 2/15
Ischemic heart disease	0
Echocardiographic data before AF ablation	
LA diameter (mm)	46.8 ± 5.4
LV end-diastolic dimension (mm)	50.6 ± 5.0
LV ejection fraction (%)	51.6 ± 5.0

ostium of the PV to eliminate the PV-LA connections.

Transthoracic echocardiography

Transthoracic echocardiography was performed immediately after AF ablation and then during 6–12 months of follow-up to assess the LA diameter, LVEDD, and LVEF. LA diameter was measured in the parasternal long axis view.

Follow-up

All patients were hospitalized for several days after AF ablation for titration of oral anticoagulant therapy to the international normalization ratio of 1.5 to 2.5 and were monitored telemetrically. After discharge, all patients visited our outpatient clinic at 2- to 4-week intervals. A standard ECG was recorded at each visit. When patients presented with any symptoms suggestive of paroxysmal AF recurrence, a 24-hour Holter ECG was additionally performed. If there was paroxysmal AF recurrence, AAD therapy was initiated after spontaneous AF termination or DC cardioversion. If the paroxysmal AF was not controlled by AAD within 3 months, the patients were offered further AF ablation. If the patient had no symptoms at 3 months after AAD therapy, they were offered the option of discontinuing AAD to exclude the possibility of false AF recurrence in the blind period immediately after AF ablation.

Statistical analysis

The continuous variables have been expressed as the mean ± standard deviation (SD). Analyses of the changes in the hemodynamic parameters and echocardiographic parameters were made conducted using the paired *t*-test or the Wilcoxon signed-ranks test. Pearson's correlation coefficient was used for correlation analyses.

$P < 0.05$ was considered to be statistically significant.

Results

Study population

The baseline characteristics of the study subjects are displayed in **Table**. Hypertensive heart disease and dilated cardiomyopathy was present in 3 (20%) and 2 patients (13%), respectively, and none of the patients had ischemic heart disease.

The mean dilated LA diameter was 46.8 ± 5.4 mm at baseline. The peak flow velocity at the ostium of the LA appendage reduced to 0.28 ± 0.14 m/s on the transesophageal echocardiography.

In 6/15 (40%) patients, DC cardioversion failed to restore sinus rhythm during a few months before AF ablation.

Procedural outcome

The mean volume of the 3D LA geometry constructed by the CARTO system was 108.1 ± 24.6 ml. The mean procedure time was 311 ± 56 minutes (range, 270–480 minutes). More than 2 CFAE sites were recorded in all 15 patients. CFAEs were identified most frequently around the PV ostium (15 patients, 100%), followed by the anterior wall (12 patients, 80%), the LA roof (12 patients, 80%), the LA septum (10 patients, 66.7%), perimitral area (10 patients, 66.7%), and the posterior wall (8 patients, 53.3%).

Figure 1 shows the AF ablation results from the procedure up to 12 months of followup. The mean followup duration was 17.7 ± 7.2 months (range, 12–37 months).

In a single patient, AF was terminated during CFAE ablation at the anterior wall of the LA. Conversion of AF to polymorphic AFL was observed in 1 patient. AFL could not be terminated by the ablation procedures. Eventually, DC cardioversion was performed to restore sinus rhythm after AF ablation in the remaining 14 patients. Of these 14 patients, 2 had a history of AF for more than 5 years. These 2 patients were administered 50 mg of flecainide intravenously in order to facilitate DC cardioversion, and oral flecainide (100 mg/day) therapy was initiated to avoid early AF recurrence.

Paroxysmal AF recurred in 5 (33%) patients during the first 2 weeks after AF ablation and in 4 (26.7%) patients after this period. AF spontaneously terminated and did not persist in all but 1 of the 9 patients in which DC cardioversion was performed.

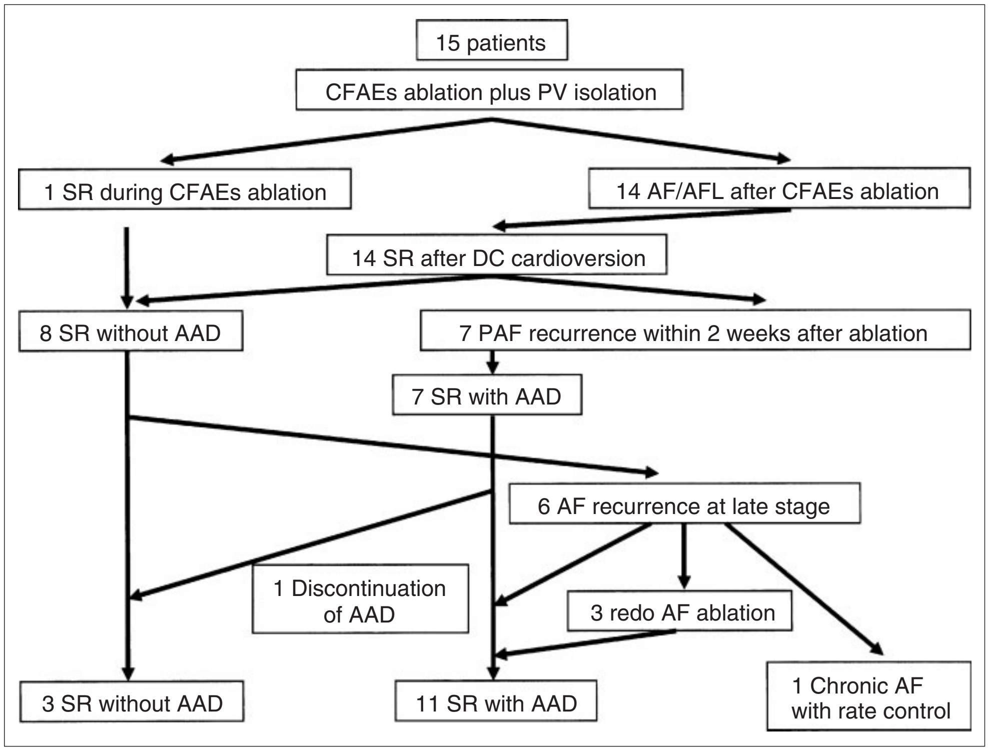

Figure 1 This tree shows in detail the AF ablation results for 15 patients with chronic atrial fibrillation (>1 year).
SR: sinus rhythm, AFL: atrial flutter, AAD: antiarrhythmic drug therapy, PAF: paroxysmal AF.

AAD therapy was initiated in these 9 patients—5 on bepridil (50∼100 mg/day), 1 on flecainide (100 mg/day), 1 on pilsicainide (75 mg/day), 1 on aprindine (15 mg/day), and 1 on amiodarone (200 mg/dl). In 4 of these 9 patients, paroxysmal AF appeared frequently. Of these, 3 patients underwent second procedure (20%). One patient did not wish to undergo the second procedure, and therefore was given rate-control therapy.

At 12 months of follow-up after AF ablation, paroxysmal AF was successfully controlled with and without AAD in 11 (73.3%) patients and 3 (20%) patients, respectively. There were no adverse effects from AAD during the follow-up period.

Complications

Over a total of 18 sessions, the following complications were observed: deterioration of congestive heart failure ($n = 1$), transient ischemic neurogenic attack ($n = 1$), and partial right phrenic nerve damage ($n = 1$). All problems resolved completely within a few days.

Changes in the hemodynamic parameters after AF ablation

In 10/15 patients who underwent AF ablation (66.7%), the hemodynamic parameters before and immediately after AF ablation were compared. The changes in the mean heart rate (before and immediately after AF ablation: 78.9 ± 18.4/minute and 88.7 ± 17.4/minute, respectively; $P = 0.1$) and pulmonary capillary wedge pressure (before and immediately after AF ablation: 12.5 ± 5.5 mmHg and 12.3 ± 6.4 mmHg, respectively; $P = 0.89$) were not significant. The cardiac index significantly increased immediately after AF ablation in all the study subjects (before and immediately after AF ablation: 2.3 ± 0.34 l/minute/m^2 and 3.5 ± 0.6 l/minute/m^2, respectively; $P < 0.01$). The stroke volume index tended to increase (before and immediately after AF ablation: 31.3 ± 7.7 ml/m^2 and 38.4 ± 7.2 ml/m^2, respectively; $P = 0.05$) (**Figure 2**).

Changes in the transthoracic echocardiographic data after AF ablation

In 14 patients in whom sinus rhythm was maintained, the LA diameter significantly decreased from 46.8 ± 5.4 mm at baseline to 42.0 ± 4.2 mm at 12 months of follow-up ($P < 0.05$) (**Figure 3**). Neither the LV end-diastolic diameter nor the LV ejection fraction changed during 12 months of follow-up.

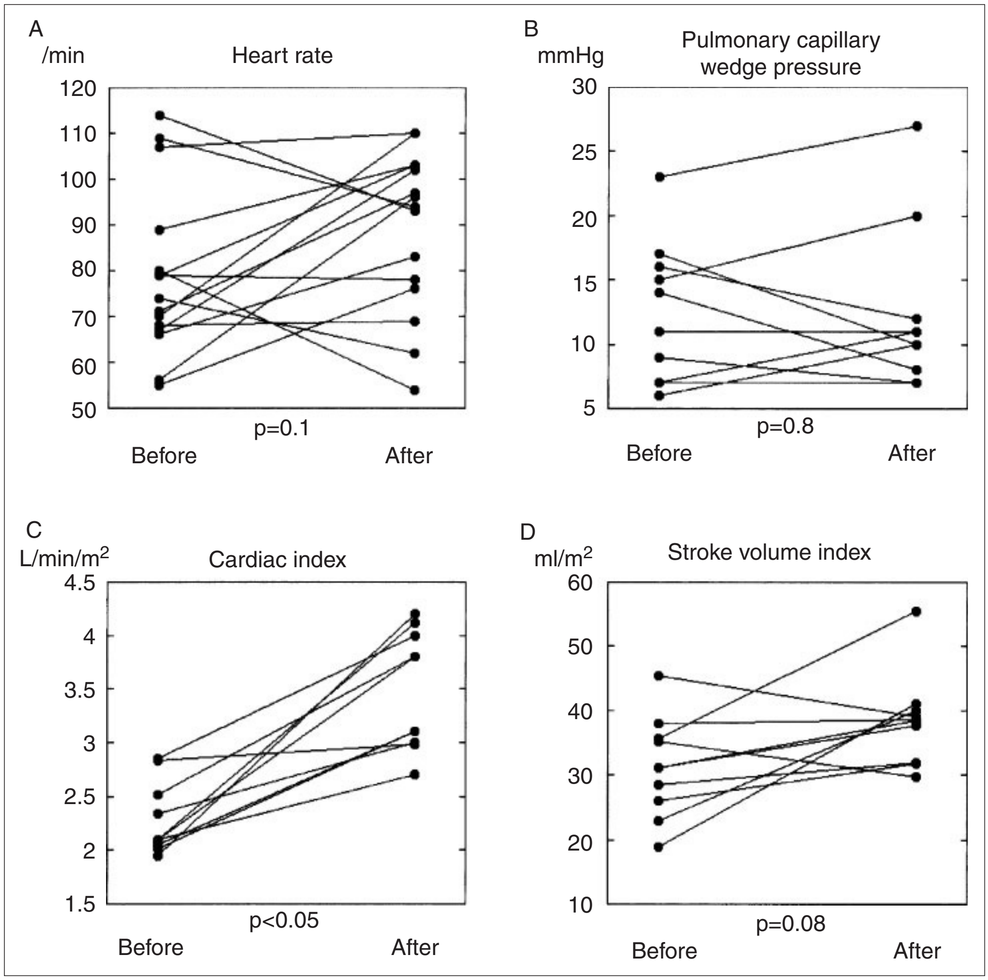

Figure 2 Changes in the hemodynamic parameters before and immediately after the AF ablation.
A (upper left): Heart rate, B (upper right): Pulmonary capillary wedge pressure, C (lower left): Cardiac index, D (lower right): Stroke volume index

Discussion

We showed that CFAE ablation plus PV isolation with DC cardioversion successfully restored sinus rhythm in all 15 chronic AF cases; in 6 of these cases, prior attempts of DC cardioversion had been unsuccessful. CFAE ablation plus PV isolation enabled the maintenance of sinus rhythm in all patients, although 11/15 patients (73.3%) required AAD therapy for 17.7 ± 7.2 months. During the 12-month follow-up period, LA diameter significantly decreased from the baseline value.

Significance of CFAEs in the ablation strategy for chronic AF

Recent studies have reported that PV isolation can control AF without the need for AAD therapy by eliminating the AF trigger in approximately 80% of patients with paroxysmal AF.[16] However, in patients with a history of persistent AF, structural remodeling possibly exists in the LA; therefore, substrate modification is considered to be necessary for ablation of persistent AF.[7,8,11–13]

Currently, various ablation techniques to modify AF substrates have been proposed for treatment of persistent AF.[8–13] Nademanee et al. demonstrated that ablation targeting CFAEs restored sinus rhythm in 62% of patients with chronic AF and produced a long-term success rate of 77%.[10] In contrast, Oral et al. revealed that ablation guided by CFAEs resulted in the conversion of AF to sinus rhythm in only 16% of patients with chronic AF, and then, the rate of sinus rhythm was maintained at 57%.[17] The significance of CFAEs in ablation for chronic AF remains to be studied. In the present study, AF was converted to sinus rhythm in 1 patient and to polymorphic AFL in 1 patient during CFAE ablation after PV isolation. Sinus rhythm was maintained

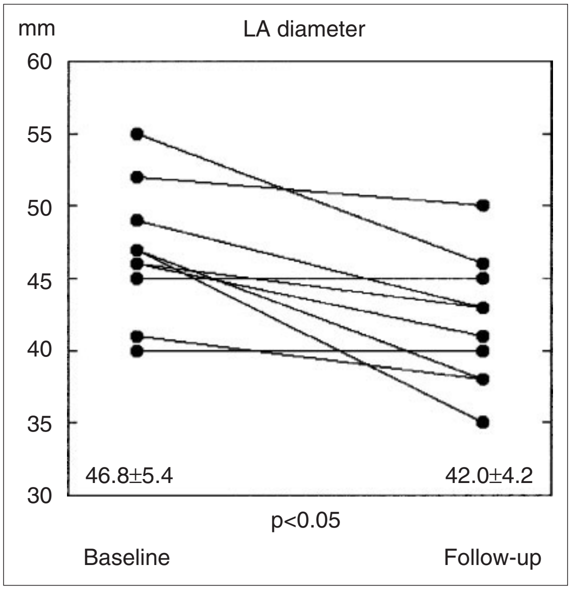

Figure 3 Changes in the LA diameter before AF ablation to follow-up.

without the need for AAD therapy in 20% of the patients and with AAD in 73.3% of the patients. Although the AF conversion rate in this study was similar to that reported by Oral et al.,[17] the long-term success rate without AAD was less than that reported by other investigators.[10,17] This discrepancy might be derived from the difference in the maximum power of RF used in both studies. They used a maximum power of 70 W as compared to the maximum power of 35 W used in the present study.

On the other hand, in the RACE trial in which a strict protocol involving AAD with DC cardioversion was adopted for the rhythm control group, sinus rhythm was maintained in only 39% of the subjects of that group.[15] In the present study, maintenance of sinus rhythm was observed in a greater percentage of study subjects than in the rhythm control group of the RACE trial. Accordingly, it was thought that CFAE ablation plus PV isolation was potentially more useful than AAD therapy alone for long-term maintenance of sinus rhythm in chronic AF patients.

Significance of maintenance of sinus rhythm in the recovery of cardiac function

Haissaguerre et al. demonstrated that the restoration and maintenance of sinus rhythm by catheter ablation without AAD improved cardiac function, including an improvement in LVEF and decrease in the LA diameter among patients with congestive heart failure and AF, mainly chronic AF.[13)]

In that study, patients with adequate rate control also benefited from catheter ablation; this finding demonstrates that ablation produced the additional hemodynamic benefits from the restoration of sinus rhythm rather than pharmacological rate control.

In the present study, we also revealed that the LA diameter significantly decreased by $9.5 \pm 8.1\%$ during 12-months follow-up period. Beukema et al. revealed that AF recurrence after AF ablation was associated with an increase in the LA diameter and that there was a significant relationship between the success in the maintenance of sinus rhythm and the decrease in the LA diameter.[18] Since the LA diameter was shown to decrease significantly in the present study, it was conceivable that our strategy was truly effective in maintaining sinus rhythm.

In the present study, AAD therapy had no adverse effects at the doses used during the follow-up period. However, the AFFIRM and RACE trials have shown that the adverse effects of AAD offset the benefits of the maintenance of sinus rhythm in cases where it is used for the maintenance of sinus rhythm.[15,19] Therefore, careful attention should still be paid to adverse effects of AAD, particularly in the long run.

Conclusion

We observed that maintenance of sinus rhythm by CFAE ablation plus PV isolation led to the recovery of the structural changes in the LA, despite the fact that AAD therapy was required in some cases.

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